Cashew

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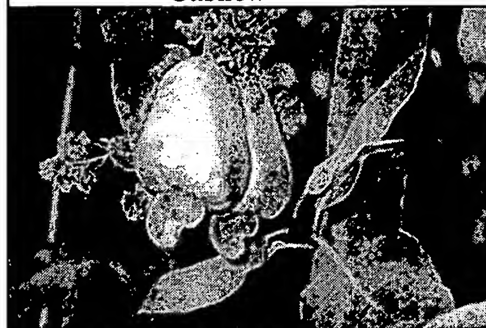
Cashew

Cashews ready for harvest in Guinea
Scientific classification

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Sapindales
Family:	Anacardiaceae
Genus:	*Anacardium*
Species:	***A. occidentale***

Binomial name
Anacardium occidentale L.

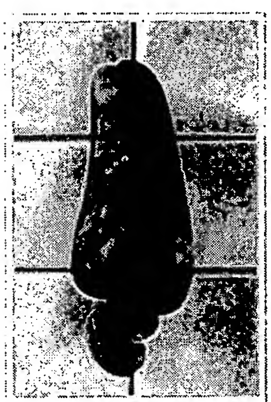
The **Cashew** (*Anacardium occidentale*) is a tree in the flowering plant family Anacardiaceae. The plant is native to northeastern Brazil, where it is called by its Portuguese name *Caju* (the fruit) or *Cajueiro* (the tree). It is now widely grown in tropical climates for its cashew nuts and cashew apples. Originally spread from Brazil by the Portuguese, the cashew tree today can be found in all regions with a sufficiently warm and humid climate.

Anacardium occidentale, from Koehler's *Medicinal-Plants* (1887)

What appears on the tree to be the fruit of the cashew tree is an oval to pear-shaped accessory fruit or false fruit that develops from the receptacle of the cashew flower. Called the **cashew apple**, better known in Panama as "**marañón**", it ripens into a yellow and/or red structure about the size of a plum or pear (5–11 cm).

The true fruit of the cashew tree is a roughly kidney-shaped or boxing-glove shaped drupe that grows at the end of the pseudofruit. Actually, the drupe develops first on the tree, and then the peduncle expands into the pseudofruit. Within the true fruit is a single seed, the **cashew nut**. Although a nut in the culinary sense, in the botanical sense the fruit of the cashew is a seed. However, the true fruit is classified as a nut by some botanists. The seed is surrounded by a double shell containing a caustic phenolic resin. Some people are allergic to cashews, but cashews are a less frequent allergen than some other nuts.

Uses

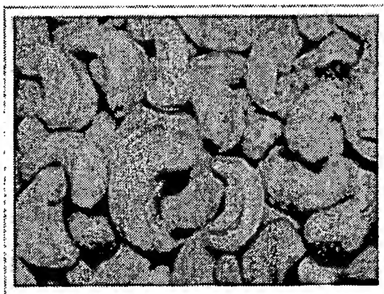


The cashew apple is used for its juicy but acidic pulp, which can be eaten raw or used in the production of jam, chutney, or various beverages. Depending on local customs, its juice is also processed and distilled into liquor or consumed diluted and sugared as a refreshing drink. In Goa, India, the cashew apple is the source of juicy pulp used to prepare *fenny*, a locally popular distilled liquor. The cashew apple contains much tannin and is very perishable. For this reason, in many parts of the world, the false fruit is simply discarded after removal of the cashew nut.

Cashew fruit contains a potent skin irritant toxin called urushiol (also found in poison-ivy) within the dark green nut shells. This must be removed when the seed inside is processed for consumption; this is done by shelling the nuts, a somewhat hazardous process, and exceedingly painful skin rashes (similar to poison-ivy rashes) among

Cashew fruit

processing workers are common. In India urushiol is traditionally used to control tamed elephants by its mahout (rider or keeper). The so-called "raw cashews" available in health food shops have been cooked but not roasted or browned.


cashew nut snack, roasted and salted

Cashew nuts are a common ingredient in Asian cooking, for example, in dishes such as "chicken with cashews". They can also be ground into a spread called cashew butter similar to peanut butter. Cashews have a very high oil content, and they are used in some other nut butters to add extra oil. In an off-the-shelf package of cashews found in the United States, a 30-gram serving contained 180 calories (750 kilojoules), 70% of which was fat.

The liquid contained within the shell casing of the cashew, known as Cashew Nutshell Liquid (CNSL), has a variety of industrial uses which were first developed in the 1930s. CNSL is fractionated in a process similar to the distillation of petroleum, and has two primary end products: solids that are pulverized and used as friction particle for brake linings, and an amber-colored liquid that is aminated to create phenalkamine curing agents and resin modifiers. Phenalkamines are primarily used in epoxy coatings for the marine and flooring markets, as they have intense hydrophobic properties and are capable of remaining chemically active at low temperatures.

References and external links

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- Cajueiro - Tropical plant database by Raintree Nutrition (http://www.rain-tree.com/cajueiro.htm)
- History of the industrial use of Cashew Nutshell Liquid (http://www.cardolite.com/www/cnsl_history.htm)
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- Kent's Lectures on Homeopathic Materia Medica: Anacardium orientale (anac.) (http://www.homeoint.org/books3/kentmm/anac.htm)
- A Primer of Materia Medica for practitioners of Homœopathy: Anacardium (http://www.homeoint.org/books5/allenprimer/anac.htm)
- Research Paper on the Cashew Processing Industry in West Africa (http://organiccashewnuts.com/cashewresearch.htm)

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Article

Utilisation of Cashew Nut Shell Liquid from *Anacardium occidentale* as Starting Material for Organic Synthesis: A Novel Route to Lasiodiplodin from Cardols

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Como parte de nosso programa envolvendo a utilização do LCC (Líquido da Casca da Castanha), obtido a partir *Anacardium occidentale*, como matéria-prima para preparação de compostos de maior valor agregado, descrevemos a conversão dos cardóis (6-alquenilresorcinóis) na lasiodiplodina, um macrolídeo tipo orcelínico de 12 membros, de ocorrência natural, que exibe propriedade reguladora do crescimento de plantas e atividade antileucêmica.z

As part of an ongoing program concerning utilisation of CNSL (Cashew Nut Shell Liquid) from *Anacardium occidentale* as starting material for the preparation of useful compounds, we describe the conversion of cardols (6-alkenylresorcinols) into lasiodiplodin, a naturally occurring 12-membered orsellinic acid type macrolide, which exhibits plant growth regulating and antileukemic properties.

Keywords: *Cashew Nut Shell Liquid (CNSL), lasidiplodin, cardols*

Introduction

The cashew tree, *Anacardium occidentale L*, is a botanical species native of eastern Brazil and was introduced into other tropical countries such as India, Africa, Indonesia and South East Asia in the 16th century[1]. The true fruit of cashew is the nut, a kidney shaped structure of approximately 2-3 cm in length which is attached to the end of a fleshy bulb, generally called the cashew apple. The shell comprises some 50% of the weight of the raw nut, the kernel represents 25% and the remaining 25% consists of the natural cashew nut shell liquid (CNSL), a viscous reddish brown liquid. Recently, Brazilian raw cashew nut production has increased greatly in relation to other countries. The estimated production of raw cashew nuts in Brazil for the end of this century is 290.000 tons[2]. The CNSL is traditionally obtained as a by-product during the isolation of the kernel by roasting the raw nuts, making Brazil one of the leading producers of this material.

Crude cashew nut shell liquid represents one of the major and cheapest sources of naturally occurring non-isoprenoid phenolic lipids such as anacardic acids (**1**), cardols (**2**), cardanols (**3**), methylcardols (**4**) (Fig. 1) and polymeric materials. CNSL has found important commercial usage as the phenolic raw material for the manufacture of certain resins and plastics having unusual electric and frictional properties[3].

The interesting chemical characteristics of cardols, such as the presence of a double bond at the 8-position of the long-chain in the monoene, diene and triene components and a convenient aromatic orcinol system led us to search for a strategy to convert these materials into lasiodiplodin (**5**) (Fig. 2). The latter compound is a naturally occurring 12-membered orsellinic acid type macrolide, isolated from the culture broth of the fungus *Botrydiplodia theobromae* (formally *Lasiodiplodia theobromae*), and exhibits plant growth regulating properties[4]. This macrolide has also been found in the stems and leaves of *Euphorbia splendens* and shows antileukemic activity[5]. Several total synthesis of racemic lasiodiplodin have been carried out during the last 20 years[6], while some asymmetric synthesis of the R-lasiodiplodin have been recently published[7].

Although a considerable number of procedures for the synthesis of lasiodiplodin have been disclosed, none of them have dealt with the utilisation of CNSL, a very attractive potential raw material. This study using CNSL constituents is an original contribution to the synthesis of the macrolide lasiodiplodin.

The route reported herein combined the well-established synthetic procedures (ozonolysis of double bounds;

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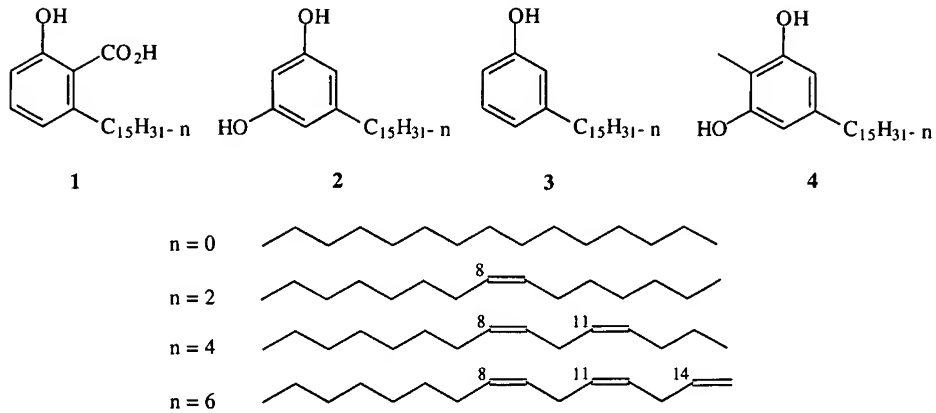


Figure 1. Naturally occurring non-isoprenoid phenolic lipids from *Anacardium occidentale*.

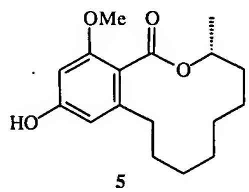


Figure 2. R-Lasiodiplodin.

regioselective carboxylation of the aromatic ring; selective methylation of one of the free phenolic groups; chemioselective oxidation of the aromatic ω-hydroxy-aldehyde and macrolactonization of ω-hydroxy–acid) for construction of lasiodiplodin from cardols.

Results and Discussion

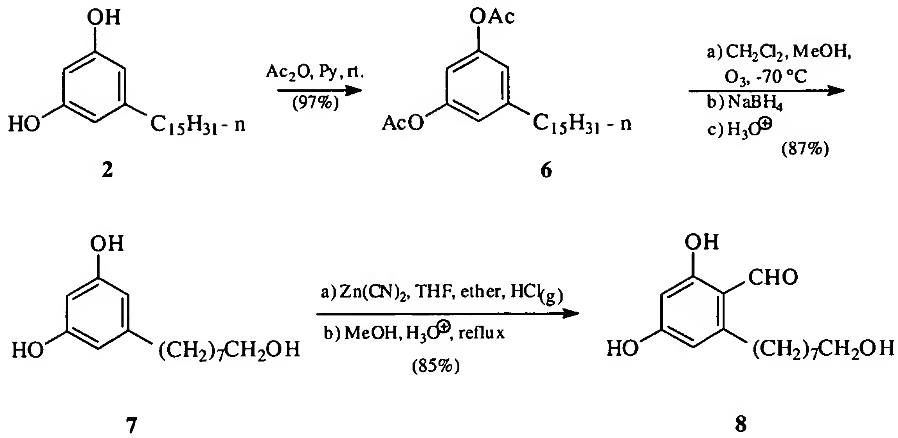
The key reaction in our initial proposal for the synthesis of lasiodiplodin was the conversion of alkenylresorcinols **2** into the corresponding substituted salicylic acids. Attempts at direct carboxylation of **2**, via the Kolbe-Schmitt and related methods failed, resulting in the recovery of unreacted **2**. Then we turned our attention to the use of the modified Gattermann reaction for indirect carboxylation, however the maximum yield obtained was not synthetically significant. The sterically hindered imide hydrochloride intermediates obtained from these phenols were not readily hydrolysed by water or dilute hydrochloric acid, but required refluxing with 10-20% hydrochloric acid. This fact suggested that the harsh conditions could chemically alter the side chains, resulting in low yields of the desired product.

We were much more successful in carrying out the desired transformation by the modified Gattermann reaction[8], using zinc cyanide and anhydrous hydrogen chloride in anhydrous THF-ethyl ether on phenol **7** furnishing the salicylic aldehyde **8** in 85% yield (Scheme 1). The compound **7** was previously prepared by ozonolysis of the acetyl derivatives **6** on multigram scales, followed by the reductive cleavage of the derived ozonides with sodium borohydride[9].

Next, we thought to carry out the indiscriminate alkylation of both phenolic functions in **8** to prepare the dimethylether **9**, followed by its transformation into diester **10**, the key intermediate used by Solladié *et al.*[7b] in the total asymmetric synthesis of both antipodes of lasiodiplodin via the asymmetric reduction of the corresponding β-ketosulfoxides.

The dimethylether **9** was prepared by treatment of phenol **8** with potassium carbonate and methyl iodide in acetone under reflux for 5 h. To our surprise several attempts at conversion of the compound **9** into the diester **10**, by treatment with potassium permanganate under many different reaction conditions, were unsuccessful, giving the desired ester in poor overall yields (15-30%). In addition, appreciable over oxidation was observed. Both potassium permanganate at room temperature and Jones reagent under normal conditions were unsatisfactory for the oxidation of **9** to the corresponding diacid, since they attacked the alcohol function without affecting the aldehyde group. Searching next for an alternative oxidative procedure for converting the hindered aldehyde group into acid group, we found that it could be readily done by using the inexpensive pair sodium chlorite-DMSO,[10] however the alcohol group was quite stable under these conditions. Since the direct oxidation of **9** to the corresponding diacid did not proceed satisfactorily, we decided to do it in a two-step process.

The effective oxidative procedure was achieved by treatment of compound **9** with PCC in methylene chloride at room temperature[11], followed by treatment with sodium chlorite-DMSO. The crude diacid was then readily esterified by methyl iodide under reflux to form the desired diester **10** in 87% overall yield (Scheme 2). Compared to the use of sodium permanganate, the two-step oxidative sequence using mild reaction conditions resulted in better overall yield. The spectral data for **10** were identical to the



Scheme 1.

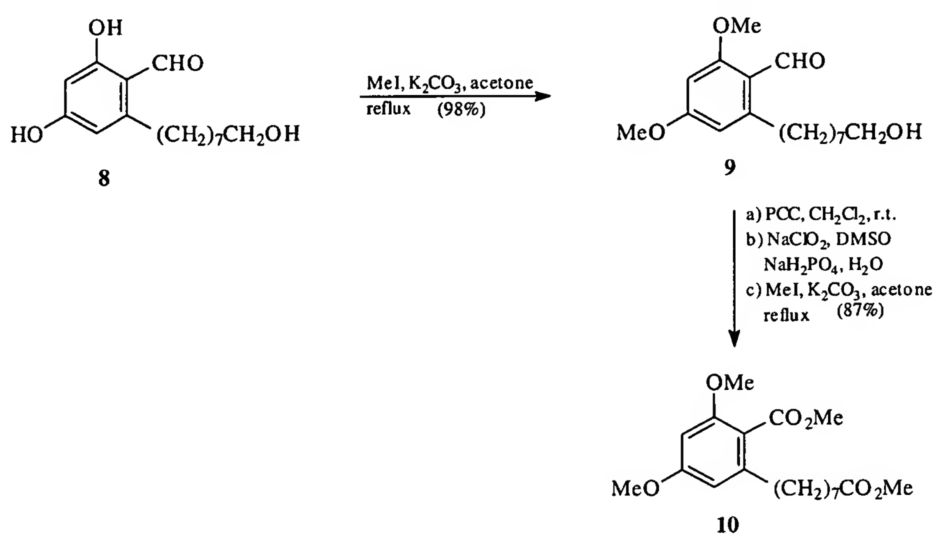
published data[7b], thus our preparation of **10** constitutes a formal synthesis of lasiodiplodin.

The recent synthetic routes to lasiodiplodin[7a-d] were achieved via the methyl ether (**10**), which has been converted into the macrolide in a multistep protocol (demethylation-benzylation-methylation-debenzylation). As we were committed to developing a simplified synthesis of lasiodiplodin, we reasoned that it should be possible to selectively protect the hydroxyl group in **8** based on an internal hydrogen-bonding effect (Scheme 3).

Application of the usual benzylation [$PhCH_2X$-K_2CO_3 (X = Cl, Br or I)] in acetone under several conditions did not lead to monoalkylation of phenol **8**, but rather gave a complex mixture of both mono- and dialkylated products along with starting material. However, when compound **8** was treated with BnCl/K_2CO_3/KI in acetone at 40 °C for 30 h, the desired monobenzylated compound **11** was afforded exclusively. The use of more drastic conditions decreased the reaction time, but also led to a decrease in selectivity. The residual phenolic hydroxyl group was methylated as described above to give **12**, which was oxidised (PCC/sodium chlorite-DMSO) and methylated to afford in high yield the unknown methyl 2-methoxy-4-benzyloxy-6-(7-methoxycarbonylheptyl) benzoate **13** (Scheme 3), a compound that we expect to be a more suitable acyclic precursor for the synthesis of both antipodes of lasiodiplodin.

Alternatively (Scheme 4), treatment of **12** with sodium chlorite-DMSO, followed by methylation furnished the ester **14** in 83% yield. The conversion into aldehyde **15** was achieved in 95% yield by treatment with PCC in methylene chloride. Treatment of the aldehyde **15** with methylmagnesium iodide afforded the hydroxyester **16**. Hydrolysis of the ester **16** required rather severe conditions, the hydroxyacid **17** being formed in 85% yield by using potassium hydroxide (10 M) in ethylene glycol at 165 °C.

In order to complete the synthesis, the hydroxyacid **17** was converted, under high dilution conditions, into lasiodiplodin benzylether **18** in 65% yield by using Mukai-



Scheme 2.

yama's procedure[12]. In the last stage, lasiodiplodin benzylether **18** was submitted to hydrogenolysis to yield quantitatively racemic macrolide, which had spectral properties identical with those reported by Gerlach[6a] (Scheme 4).

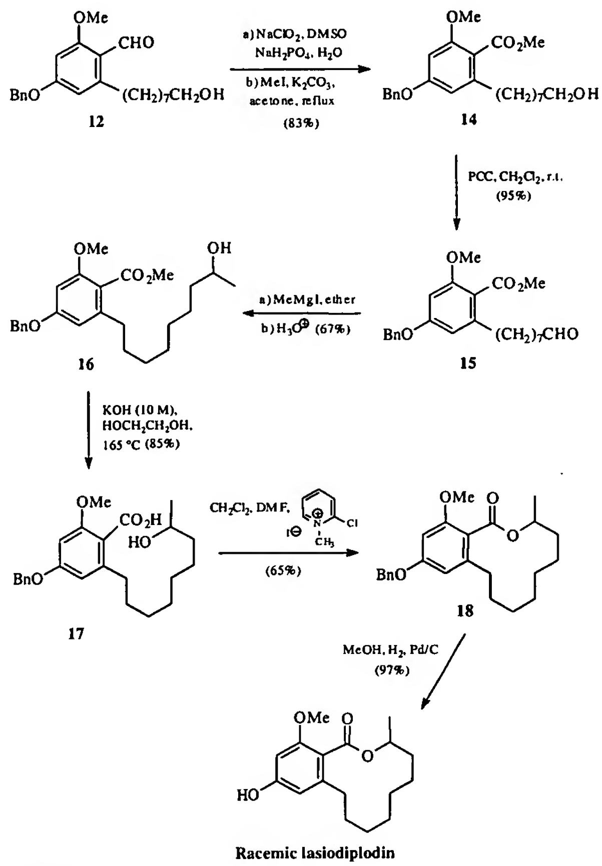
The above methodology not only constitutes a highly efficient synthesis of (±) lasiodiplodin from cardols (**2**), abundant and inexpensive natural products, but also has additional advantages over the earlier routes because of the simplicity of the chemistry involved.

Experimental

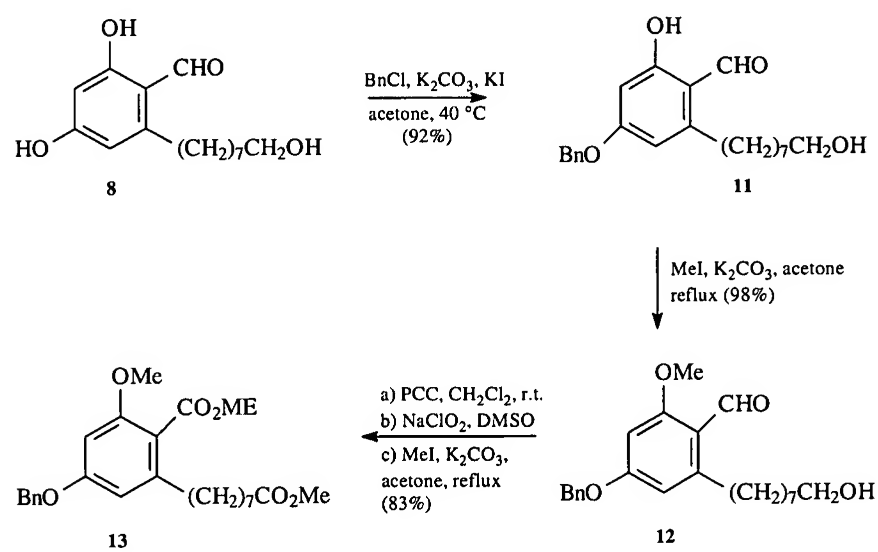
The oxidative cleavages were performed using a Welsbach T-408 ozonizer. All reactions were monitored by thin layer chromatography on silica gel ($60F_{254}$ / 0.2 mm) plates. UV light and 5% phosphomolybdic acid in ethanol, followed by heating, being used as developing agents. The purification was performed by dry-column flash chromatography on silica gel (60, particle size 0.040-0.063 mm). Melting points were determined on a Köffler apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer 283-B and Nicolet 5ZDX-FT IR spectrometers. ^{1}H-NMR spectra were recorded at 300, 200 or 90 MHz on Bruker spectrometers or a Varian EM 290 model. ^{13}C-NMR spectra were recorded at 75 and 50 MHz on Bruker spectrometers. Mass spectra were recorded on a Perkin Elmer Q-Mass 910 mass spectrometer.

Cardols

The shells (500 g) of cashew nuts from *Anacardium occidentale* (Ceará, Brazil) were extracted in a Soxhlet extractor with commercial ethanol (2.0 L), yielding a crude extract (CNSL, 157 g, 31% by weight). Anacardic acids were removed from CNSL (25 g batches) by precipitation as lead anacardates according to protocols described in the literature[13]. The resulting filtrate was concentrated to give a brown oil, which was chromatographed on silica gel by eluting with hexane-ethyl acetate mixtures of increased polarity. Cardanols (1.2 g, 4.8%), methylcardols (0.37 g,



Scheme 4.



Scheme 3.

1.5%) and cardols (6.15 g, 24.6%) were isolated sequentially.

1,3-Diacetylcardols (**6**)

To a solution of cardols (3.2 g, ~10 mmol) in acetic anhydride (20 cm^3) was added pyridine (20 cm^3). The mixture was stirred at room temperature until the reaction was shown to be complete by thin layer chromatography (hexane-ethyl acetate, 4:1, 2 h). Water was added and then the mixture was extracted with ethyl acetate. The combined extracts were washed with a cool 5% hydrochloric acid solution, brine, dried over sodium sulphate and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 4:1) to furnish **6** as a colourless oil [3.92 g, 97%]. IR (film): 3010, 2928, 2855, 1772, 1619, 1592, 1451, 1369, 1197, 1123, 1022 cm^{-1}; ^{1}H-NMR (90 MHz, CCl_4) δ: 6.75 (m, ArH), 6.1-4.8 (m, =CH, $=CH_2$), 2.9-3.6 (m, $=CCH_2C=$), 2.55 (t, $ArCH_2$), 2.15 (s, CH_3CO), 2.2-1.8 (m, $=CCH_2$), 1.8-1.1 (br, CH_2), 0.85 (t, CH_3).

2,4-Dihydroxy-6-(8-hydroxyoctyl) benzene (**7**)

A solution of **6** (3.9 g, ~9.6 mmol) in methylene chloride (50 cm^3) and methanol (50 cm^3) at -70 °C was treated with ozone until the reaction was shown to be complete by thin layer chromatography (hexane-ethyl acetate, 4:1). The reaction mixture was purged with nitrogen, sodium borohydride (~4.0 g) was added, and the resulting mixture was stirred at room temperature overnight. After addition of water, the reaction mixture was hydrolysed with 10% hydrochloric acid and then extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. The pure alcohol **7** was obtained as a white solid by recrystallization from acetone-methylene chloride [2.0 g, 87%, mp 108-110 °C]. IR (KBr): 3500-2800 (br), 2956, 2851, 1598, 1520, 1512, 1158, 1071, 1048 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ: 8.10 (s, 2H, OH), 6.17 (m, 3H, ArH), 3.81 (br, OH), 3.56 (t, 2H, CH_2O), 2.43 (t, 2H, $ArCH_2$), 1.51 (m, 4H, CH_2), 1.31 (br, 8H, CH_2); ^{13}C-NMR (75 MHz, CD_3COCD_3) δ: 159.22 (2C), 145.86, 107.71 (2C), 100.09, 62.59, 35.76, 32.81, 31.23, 29.39, 29.15, 25.83.

2,4-Dihydroxy-6-(8-hydroxyoctyl)benzaldehyde (**8**)

A 150 cm^3 three necked round-bottom flask was fitted with an adapter provided with a reflux condenser, a gas inlet tube extending nearly to the bottom of the flask and an exit tube leading to an aqueous sodium hydroxide trap. The flask was charged with the phenol **7** (1.0 g, 4.2 mmol) dissolved in THF (~5 cm^3), dry ether (100 cm^3) and powdered zinc cyanide (1.24 g, 10.5 mmol). The mixture was stirred vigorously and gaseous hydrogen chloride was passed rapidly to dissolve the zinc cyanide (20 - 30 min). Hydrogen chloride was slowly bubbled into the mixture until the reaction was shown to be complete (about 1.5 h). The solid imide intermediate was separated from the solvent by filtration and the imide hydrochloride was hydrolysed by heating for 2 h with 10-20% hydrochloric acid in methanol. After cooling, the reaction mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and evaporated. The crude mixture was chromatographed on silica gel (hexane-ethyl acetate, 3:1) to give **8** as a white solid [0.95 g, 85%, mp 68-71 °C]. IR (KBr): 3125, 2932, 2853, 1615, 1500, 1312, 1264, 1202, 1162 1058 cm^{-1}; ^{1}H-NMR (200 MHz, CD_3COCD_3) δ: 12.51 (s, 2H, ArOH), 10.09 (s, CHO), 6.30 (s, 1H, ArH), 6.16 (s, 1H, ArH), 3.91 (br, 1H, OH), 3.53 (t, 2H, CH_2O), 2.86 (t, 2H, $ArCH_2$), 1.8-1.1 (br, 12H, CH_2); ^{13}C-NMR (50 MHz, CD_3COCD_3) δ: 193.47, 166.83, 165.67, 150.52, 112.33, 110.21, 100.91, 61.95, 33.06, 32.95, 31.76, 29.98-28.98 (3C, all t), 26.06.

2,4-Dimethoxy-6-(8-hydroxyoctyl) benzaldehyde (**9**)

To a solution of the preceding arene **8** (720 mg, 2.7 mmol) in acetone (30 cm^3) was added potassium carbonate (3.7 g, 27 mmol) and methyl iodide (1.7 mL, 27 mmol). The resulting suspension was heated under reflux for 5 hours. Water was added and then the mixture was extracted with ethyl acetate. The combined extracts were washed with diluted sodium thiosulfate solution, brine and dried over sodium sulfate. After evaporation of the solvent the residue was chromatographed on silica gel (hexane-ethyl acetate, 4:1) to furnish **9** as a white solid [780 mg, 98%, mp 89-90 °C]. IR (KBr): 3395 (br), 2931, 2848, 1668, 1597, 1576, 1467, 1428, 1411, 1327, 1204, 1152 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.38 (s, 1H, CHO), 6.24 (s, 2H, ArH), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.55 (t, 2H, CH_2O), 2.86 (t, 2H, $ArCH_2$), 1.59 (s, 1H, OH), 1.45 (m, 4H, CH_2), 1.29 (m, 8H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 190.48, 165.56, 164.70, 149.85, 116.98, 108.22, 95.88, 63.19, 55.96, 55.60, 34.79, 32.95, 31.39, 29.79, 29.55, 29.44, 25.85; MS [m/z, relative intensity (%)]: 294 (M^+, 48), 279 (05), 193 (100), 180 (18), 168 (20), 152 (50).

Methyl 2,4-dimethoxy-6-(7-methoxycarbonylheptyl) benzoate (**10**)

To a suspension of PCC (110 mg, 0.51 mmol) in anhydrous methylene chloride (15 cm^3) was added hydroxyaldehyde **9** (100 mg, 0.34 mmol) in anhydrous methylene chloride (5 cm^3). The mixture was stirred at room temperature until the reaction was shown to be complete (about 2 h). The reaction mixture was quenched with anhydrous ether and filtered. The filtrate was washed with brine, dried over sodium sulphate and evaporated. To the crude residue in DMSO (5 cm^3) was added a solution of sodium chlorite (154 mg, 1.7 mmol) in water (1.5 cm^3) followed by a solution of $NaH_2PO_4.H_2O$ (235 mg, 1.7 mmol) in water

(1.5 cm^3) and the mixture was stirred at room temperature overnight. After addition of water the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. To the crude product in acetone (10 cm^3) was added potassium carbonate (470 mg, 3.4 mmol), an excess of methyl iodide (1 cm^3) and the resulting mixture was stirred under reflux for 2 h. After usual work-up, the product was chromatographed on silica gel (hexane-ethyl acetate, 9:1) to furnish **10** as a colourless oil [104 mg, 87%]. IR (film): 2936, 2856, 1732, 1605, 1459, 1432, 1268, 1203, 1159, 1100 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.31 (s, 2H, ArH), 3.87 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, OMe), 3.66 (s, 3H, OMe), 2.53 (t, 2H, $ArCH_2$), 2.29 (t, 2H, CH_2CO), 1.58 (m, 4H, CH_2), 1.3 (br, 8H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.36, 168.96, 161.49, 158.10, 143.04, 116.35, 105.90, 96.23, 55.97, 55.44, 52.14, 51.53, 34.17, 34.02, 31.06, 29.39, 29.14, 29.01, 25.03; MS [m/z, relative intensity (%)]: 352 (M^+, 25), 321 (100), 210 (65), 191 (75), 179 (17), 151 (38), 121 (08), 91 (10).

*2-Hydroxy-4-benzyloxy-6-(8-hydroxyoctyl) benzaldehyde (***11***)*

To the phenol **8** (1.35 g, 5 mmol) in dry acetone (5 cm^3) was added anhydrous potassium carbonate (691 mg, 5 mmol), anhydrous potassium iodide (830 mg, 5 mmol) and benzyl chloride (633 mg, 5 mmol). The resulting suspension was stirred at 40 °C for 30 h. After cooling, water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 3:1) to give **11** as a colourless oil [1.64 g, 92%]. IR (film): 3349, 2928, 2855, 1620, 1318, 1266, 1225, 1171, 1052 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 12.48 (s, 1H, ArOH), 10.03 (s, 1H, CHO), 7.35 (m, 5H, C_6H_5), 6.33 (s, 2H, ArH), 5.04 (s, 2H, OCH_2Ph), 3.60 (t, 2H, CH_2O), 2.78 (t, 2H, $ArCH_2$), 1.6 (br, 1H, OH), 1.54 (m, 4H, CH_2), 1.3 (br, 8H, CH_2); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 192.66, 166.40, 165.63, 142.00, 135.57, 128.58 (2C), 128.23, 127.46 (3C), 112.44, 110.11, 99.32, 70.03, 62.03, 62.74, 32.57, 32.41, 31.80, 29.19 (2C), 25.59.

*2-Methoxy-4-benzyloxy-6-(8-hydroxyoctyl) benzaldehyde (***12***)*

To the preceding benzylether **11** (1.6 g, 4.5 mmol) in acetone (50 cm^3) was added potassium carbonate (6.2, 45 mmol) and methyl iodide (2.8 mL, 45 mmol). The mixture was stirred under reflux until the reaction was shown to be complete by thin layer chromatography (hexane-ethyl acetate, 3:2). After 4 h water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. The residue was chromatographed on silica gel (hexane-ethyl acetate, 4:1) to give **12** as a pale yellow oil [1.63 g, 98%]. IR (film): 3407, 2929, 2855, 1674, 1598, 1456 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 10.43 (s, 1H, CHO), 7.55-7.15 (m, 5H, C_6H_5), 6.38 (s, 2H, ArH), 5.08 (s, 2H, OCH_2Ph), 3.81 (s, 3H, OMe), 3.56 (t, 2H, CH_2O), 2.91 (t, 2H, $ArCH_2$), 2.54 (s, 1H, OH), 1.52 (m, 4H, CH_2), 1.30 (br, 8H, CH_2); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 190.24, 165.21, 163.57, 149.59, 135.93, 128.64 (2C), 128.24, 127.52 (2C), 116.81, 108.67, 96.46, 70.04, 62.85, 55.70, 34.52, 32.68, 31.08, 29.49, 29.30, 29.21, 25.60.

*Methyl 2-methoxy-4-benzyloxy-6-(7-methoxycarbonyl-heptyl) benzoate (***13***)*

To a suspension of PCC (110 mg, 0.51 mmol) in anhydrous methylene chloride (15 cm^3) was added the hydroxyaldehyde **12** (126 mg, 0.34 mmol) in anhydrous methylene chloride (5 cm^3). The mixture was stirred at room temperature for about 2 hours. The reaction mixture was quenched with anhydrous ether and filtered. The filtrate was washed with brine, dried over sodium sulphate and evaporated. To the crude residue in DMSO (5 cm^3) was added a solution of sodium chlorite (154 mg, 1.7 mmol) in water (1.5 cm^3) followed by a solution of $NaH_2PO_4.H_2O$ (235 mg, 1.7 mmol) in water (1.5 cm^3) and stirred at room temperature overnight. After addition of water, the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. To the crude product in acetone (10 cm^3) was added potassium carbonate (470 mg, 3.4 mmol) and an excess of methyl iodide (1 cm^3). The resulting mixture was stirred under reflux for 2 h. After usual work-up the product was chromatographed on silica gel (hexane-ethyl acetate, 9:1) to furnish **13** as a colourless oil [121 mg, 83%]. IR (film): 2934, 2857, 1732, 1603, 1456, 1432, 1268, 1194, 1160 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.45-7.22 (m, 5H, C_6H_5), 6.38 (s, 2H, ArH), 5.04 (s, 2H, OCH_2Ph), 3.82 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.54 (t, 2H, $ArCH_2$), 2.28 (m, CH_2CO), 1.55 (m, 4H, CH_2), 1.27 (br, 8H, CH_2); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 174.28, 168.82, 160.48, 157.88, 142.85, 136.52, 128.59 (2C), 128.07, 127.53 (2C), 116.34, 106.63, 96.94, 70.04, 55.82, 52.08, 51.44, 34.04, 33.84, 31.03, 29.19 (3C, all t), 24.88.

*Methyl 2-methoxy-4-benzyloxy-6-(8-hydroxyoctyl) benzoate (***14***)*

To a solution of the hydroxyaldehyde **12** (1.0 g, 2.7 mmol) in DMSO (20 cm^3) was added a solution of sodium chlorite (610 mg, 5.4 mmol) in water (5 cm^3) followed by a solution of $NaH_2PO_4.H_2O$ (745 mg, 5.4 mmol) in water (5 cm^3). The mixture was stirred a room temperature overnight. After addition of water, the mixture was extracted with ethyl acetate. The combined extracts were washed

with brine, dried over sodium sulphate and evaporated. To the crude product in acetone (10 cm^3) was added potassium carbonate (3.7 g, 27 mmol) and methyl iodide (1.68 cm^3, 27 mmol). The resulting mixture was stirred under reflux for 2 h. After usual work-up the product was chromatographed on silica gel (hexane-ethyl acetate, 9:1) to furnish **14** [897 mg, 83%]. IR (film): 3417, 2930, 2855, 1726, 1604, 1456, 1431, 1270, 1161 cm^{-1}; ^{1}H-NMR (50 MHz, $CDCl_3$) δ: 7.60-7.10 (m, 5H, C_6H_5), 6.38 (s, 2H, ArH), 5.03 (s, 2H, OCH_2Ph), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.60 (t, 2H, CH_2O), 2.51 (t, 2H, $ArCH_2$), 1.5 (m, 5H, OH, CH_2), 1.28 (br, 12H, CH_2); ^{13}C-NMR (200 MHz, $CDCl_3$) δ: 168.82, 160.42, 157.82, 142.86, 136.46, 128.53 (2C), 128.01, 127.47 (2C), 116.63, 96.87, 70.01, 62.86, 55.76, 52.02, 33.81, 32.64, 30.97, 29.25 (3C, all t), 25.59.

Methyl 2-methoxy-4-benzyloxy-6-(8-oxo-octyl) benzoate (**15**)

To a suspension of PCC (685 mg, 3.18 mmol) in anhydrous methylene chloride (20 cm^3) was added the hydroxyester **14** (850 mg, 2.12 mmol) in anhydrous methylene chloride (10 cm^3). The mixture was stirred at room temperature for 2 hours. Anhydrous ether was added and the resulting mixture was filtered. The filtrate was washed with brine, dried over sodium sulphate and evaporated. The crude residue was filtered on silica gel to give **15** (803 mg, 95%). IR (film): 2932, 2858, 1725, 1604, 1456, 1432, 1269, 1160 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.73 (s, 1H, CHO), 7.60-7.10 (m, 5H, C_6H_5), 6.38 (s, 2H, ArH), 5.03 (s, 2H, OCH_2Ph), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.46 (t, 2H, $ArCH_2$), 2.39 (t, 2H, CH_2CO), 2.85-2.30 (m, 4H, CH_2), 1.27 (br, 8H, CH_2); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 202.89, 168.76, 160.42, 157.82, 142.74, 136.46, 128.53 (2C), 128.01, 127.47 (2C), 116.28, 106.58, 98.88, 69.97, 55.76, 52.01, 43.77, 33.76, 30.92, 29.07 (2C), 28.91, 21.92.

(±) Methyl 2-methoxy-4-benzyloxy-6-(8-hydroxynonanyl) benzoate (**16**)

A solution of methylmagnesium iodide (~2.2 mmol) in anhydrous ether (5 cm^3) was slowly added at 0 °C to a solution of the preceding aldehyde **15** (750 mg, 1.88 mmol) in anhydrous ether (20 cm^3). At the end of addition, the reaction mixture was refluxed for 2 h. After the addition of ether, the reaction mixture was hydrolysed with a 5% hydrochloric acid solution and extracted with ether. The combined extracts were washed with a 5% sodium thiosulphate, sodium bicarbonate and brine. The organic phase was dried over sodium sulphate and after evaporation of the solvent, the residue was chromatographed on silica gel (hexane-ethyl acetate, 3:1) to give **16** [523 mg, 67%]. IR (film): 3413, 2931, 2856, 1726, 1604, 1455, 1432, 1270, 1160 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.50-7.20 (m, 5H, C_6H_5), 6.38 (s, 2H, ArH), 5.03 (s, 2H, OCH_2Ph), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.60-4.00 (m, 1H, OCH), 2.51 (t, 2H, $ArCH_2$), 1.52 (t, 2H, CH_2CO), 1.27 (br, 10H, CH_2), 1.50 (d, 3H, CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 168.82, 160.82, 157.82, 142.89, 136.46, 128.53 (2C), 128.03, 127.47 (2C), 116.28, 106.59, 96.99, 69.99, 68.07, 55.76, 52.03, 39.19, 33.81, 30.98, 29.36, 29.26, 29.08, 25.63, 23.34.

(±) 2-Methoxy-4-benzyloxy-6-(8-hydroxynonanyl) benzoic acid (**17**)

To a solution of the hydroxyester **16** (450 mg, 1.08 mmol) in ethylene glycol (15 cm^3) was added a 10 M potassium hydroxide solution (2 cm^3). After stirring at 165 °C for 2 h under a nitrogen atmosphere, the reaction mixture was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulphate and evaporated. After chromatography on silica gel (hexane-ethyl acetate, 1:1), hydroxyacid **17** was obtained as a viscous oil (370 mg, 85%). IR (film): 3600-2500 (br), 2931, 1704, 1604, 1455, 1162 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.50-7.20 (m, 5H, C_6H_5), 6.43 (s, 1H, ArH), 6.40 (s, 1H, ArH), 5.60-5.10 (br, 1H, OH), 5.04 (s, 2H, OCH_2Ph), 4.00-3.50 (m, 1H, OCH), 3.81 (s, 3H, OMe), 2.71 (t, 2H, $ArCH_2$), 1.55 (m, 4H, CH_2CO, CH_2), 1.29 (br, 8H, CH_2), 1.15 (d, 3H, CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 169.98, 160.83, 158.52, 145.57, 136.28, 128.59 (2C), 128.12, 127.49 (2C), 114.33, 107.81, 97.02, 70.02, 68.17, 58.06, 38.96, 34.42, 30.98, 29.02, 28.88 (2C), 25.35, 23.28.

(±) Lasiodiplodin-benzylether (**18**)

To a refluxing solution of 2-chloro-1-methylpyridinium iodide (792 mg, 3.1 mmol) in methylene chloride (50 cm^3) and acetonitrile (15 cm^3) was continuously and uniformly added a solution of hydroxyacid **17** (250 mg, 0.62 mmol) and triethylamine (0.86 cm^3, 6.2 mmol) in methylene chloride (50 cm^3) over a period of 10 h. After complete addition, the reaction mixture was refluxed for an additional 2 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed with water, diluted phosphoric acid solution, saturated sodium bicarbonate solution, brine and dried over sodium sulphate. The organic phase was concentrated to give a pale yellow residue which was chromatographed on silica gel (hexane-ethyl acetate, 9:1) to afford **18** [156 mg, 65%]. IR (film): 2931, 2857, 1716, 1604, 1455, 1422, 1376, 1264, 1193, 1160, 1092, 1027 cm^{-1}; ^{1}H-NMR (90 MHz, CCl_4) δ: 7.35 (m, 5H, C_6H_5), 6.29 (s, 2H, ArH), 5.30-4.90 (m, 1H, HCO), 4.95 (s, 2H, OCH_2Ph), 3.68 (s, 3H, OMe), 3.00-2.00 (m, 2H, $ArCH_2$), 1.90-1.00 (br, 12H, CH_2), 1.20 (d, 3H, CH_3).

(±) Lasiodiplodin

To a solution of (±) lasiodiplodin-benzylether **18** (120 mg, 0.3 mmol) in methanol (10 cm^3) were added two drops of acetic acid and 10% palladium on carbon (100 mg). The mixture was maintained under a hydrogen atmosphere (4 atm) until the reaction was shown to be complete by chromatography (hexane-ethyl acetate, 4:1). After 3 h, the reaction mixture was filtered. The clean filtrate was concentrated under reduced pressure and the residue was purified by chromatography (hexane-ethyl acetate 9:1) to furnish racemic lasiodiplodin (89 mg, 97%). IR (film): 3376, 2933, 2859, 1606, 1464, 1349, 1193, 1089 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.05 (br, OH), 6.28 (s, 2H, ArH), 5.25 (m, 1H, OCH), 3.65 (s, 3H, OMe), 2.80-2.30 (m, 2H, $ArCH_2$), 2.00-1.60 (m, 2H, $ArCH_2\underline{CH_2}$), 1.60 (m, 4H, CH_2), 1.50 (br, 6H, CH_2), 1.30 (d, 3H, CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 189.65, 158.06, 157.82, 142.90, 116.70, 108.41, 96.94, 72.60, 55.65, 32.25, 30.31, 30.02, 26.30, 25.40, 24.05, 21.26, 19.45; MS [m/z, relative intensity (%)]: 292 (M^+, 83), 191 (08), 182 (100), 177 (40), 164 (18), 138 (70), 69 (13), 55 (22).

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